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US-A- 4 469 677
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US-A- 4 565 696
US-A- 4 599 230

CELL, vol. 44, March 1986; TOWNSEND et al., pp. 959-968&NUM;

(73) Proprietor: **MASSACHUSETTS INSTITUTE OF TECHNOLOGY**
77 Massachusetts Avenue
Cambridge, MA 02139 (US)

(72) Inventor: **GEFTER, Malcolm, L.**
27 Coburn Road
Weston, MA 02193 (US)
Inventor: **GUILLET, Jean-Gerard**
536 Mt. Auburn Street
Watertown, MA 02172 (US)

(74) Representative: **Ford, Michael Frederick et al**
MEWBURN ELLIS
York House
23 Kingsway
London WC2B 6HP (GB)

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substantially inactivated. By contrast, by varying the consensus sequence for binding to the transplantation antigens of the target host(s) one can activate specifically one or a few subsets of lymphocytes to provide for a stimulated immune system for purposes of vaccination, enhanced response to a pathogenic invader, or other event associated with protection by the immune system. In addition, one can modulate the autoimmune system by inactivating lymphocytes associated with attack on native tissue. Thus, there is an extensive spectrum of uses of the subject invention for enhancing or diminishing particular cells in relation to their function.

Claims

1. A composition containing a molecule consisting of a first domain of at least an 8 amino acid sequence and not more than a 100 amino acid sequence of an immunodominant sequence of a first antigen, or a mutated sequence thereof, said sequence being restricted by a transplantation antigen, wherein said mutation results in greater conformity with the consensus sequence of an agretope restricted by said transplantation antigen, or said first domain consists of a sequence consisting essentially of a sequence of at least 8 amino acids and not more than 100 amino acids of a polymorphic region of said first transplantation antigen;

   with the proviso that when said first domain consists of said immunodominant sequence, said domain is joined to a second epitopic site of a molecule other than said first antigen, or an epitopic site of said first antigen joined by other than the natural sequence of said first antigen,

   said composition being for use in a method for modulating the immune response of an in vivo cellular system to an epitope of said first antigen to which said cellular system is immunologically responsive, said cellular system comprising T-cells restricted by a first transplantation antigen, and cells comprising said first transplantation antigen.

2. A composition according to Claim 1, wherein said cellular system is whole blood.

3. A composition according to Claim 2, wherein said mutated sequence is mutated to conform with the consensus sequence of the agretope restricted by said transplantation antigen.

4. A composition according to Claim 1, wherein said first domain consists of a sequence of a polymorphic region of said transplantation antigen.

5. A composition according to Claim 1, wherein said first domain is joined to a second epitopic site.

6. A composition according to Claim 1 containing a further molecule comprising a first domain of at least an 8 amino acid sequence and not more than a 100 amino acid sequence of an immunodominant sequence of said first antigen, or a mutated sequence thereof, said sequence being restricted by a transplantation antigen, said mutation resulting in increased conformity with the consensus sequence of the agretope restricted by a second transplantation antigen, or said first domain consists of a sequence consisting essentially of an at least 8 amino acid sequence and not more than a 100 amino acid sequence of a polymorphic region of said second transplantation antigen,

   whereby, in an immune response modulating method, the cellular system includes heterozygous T-cells restricted by at least one of said first and second transplantation antigens, said first molecule is able to bind to said first transplantation antigen and said second molecule is able to bind to said second transplantation antigen.

7. A composition according to Claim 6, wherein said cellular system is whole blood.

8. A composition according to Claim 6, wherein said molecules are conjugated to a second epitope different from said first epitope and cross-reactive with a second antigen different from said first antigen.

9. A composition according to Claim 8, wherein said second epitope is an epitope of a pathogen.

10. A composition according to Claim 9, wherein said pathogen is a virus.

11. A composition according to Claim 9, wherein said pathogen is a parasitic organism.

12. A composition according to Claim 11, wherein said parasitic organism is *Plasmodium*.

13. A composition according to Claim 9, wherein said pathogen is a bacterium.

14. A composition containing at least one molecule consisting of a first domain of at least an 8 amino acid sequence and not more than a 100 amino acid sequence of an immunodominant sequence of a first antigen or a mutated sequence thereof, said mutation resulting in increased conformity with the consensus sequence of the agretope restricted by a transplantation antigen present, or said first domain consists of an at least an 8 amino acid sequence and not more than a 100 amino acid sequence consisting essentially of a polymorphic region of said transplantation antigen, wherein said at least one molecule is conjugated to a second epitope different from said first epitope and cross-reactive with a second antigen different from said first antigen, said at least one molecule being bindable to its respective transplantation antigen, whereby the composition is useful to modulate the immune response of a mammalian host to an epitope of a first antigen to which the host is responsive, said mammalian host having homozygous or heterozygous T-cells restricted by at least one transplantation antigen, and the host having homozygous cells comprising said transplantation antigen or heterozygous cells comprising a first and a second transplantation antigen, each of said transplantation antigens being responsive to a consensus sequence.

15. A composition comprising two molecules for modulating the immune response of lymphocytes having transplantation antigens to a first epitope of a first antigen, each of which molecules is characterized in that it consists of a first domain consisting of at least an 8 amino acid sequence and not more than a 100 amino acid sequence of an immunodominant sequence of said first antigen, or a mutated sequence thereof, restricted by said transplantation antigens, said mutation resulting in increased conformity with a consensus sequence of different agretopes restricted by said transplantation antigens or a sequence consisting essentially of a polymorphic region of said transplantation antigens;
wherein each of said molecules specifically binds to different transplantation antigens.

16. A composition according to Claim 15, wherein said molecules are characterized in that they consist of a mutated sequence of said immunodominant sequence conjugated to a sequence comprising a second epitope different from said first epitope and cross-reactive with a second antigen different from said first antigen.

17. A composition according to Claim 15, wherein each of said molecules is of fewer than 100 amino acids.

18. A composition according to Claim 15, wherein each of said molecules is of fewer than 30 amino acids.

19. A composition according to Claim 15, wherein said molecules are characterized in that they consist of said consensus sequence.

20. A composition according to Claim 15, wherein said first antigen is an antigen of a pathogen.

21. A composition containing at least one molecule consisting of a mutated sequence of at least 8 and not more than 100 amino acids of an immunodominant sequence of a first antigen joined to a sequence defining an epitopic site of a first antigen or a second antigen different from said first antigen.

22. A composition according to Claim 21, wherein said epitopic site is of said second antigen, and said second antigen is an antigen of a pathogen, an oncogene, a transplantation antigen, or a lipopolysaccharide.

23. A composition comprising a sequence of at least 8 amino acids and not more than 100 amino acids of an immunodominant sequence of a first antigen joined to a sequence defining an epitopic site of a different second antigen.

24. A composition containing at least one molecule consisting of a mutated sequence of at least 8 amino acids and not more than 100 amino acids of an immunodominant sequence of a first antigen, said mutation resulting in increased conformity with the consensus sequence of an agretope restricted by a transplantation antigen.

25. A composition containing at least one molecule consisting of a mutated sequence of at least 8 amino acids and not more than 100 amino acids of an immunodominant sequence of a first antigen, said mutation resulting in a sequence capable of activating a particular subset of T cells or of preventing activation of a particular subset of T cells.

26. A composition containing at least one molecule consisting of a mutated sequence of at least 8 amino acids and not more than 100 amino acids of an immunodominant sequence of a first antigen, whereby the composition is useful to modulate the immune response of a mammalian host to an epitope of said first antigen to which the host is responsive.

27. Use of a composition according to any of claims 14, 23, 24, 25 or 26, for the manufacture of a medicament for modulating an immune response of an individual.

Patentansprüche

1. Zusammensetzung, die ein Molekül enthält, das aus einer ersten Domäne aus einer Sequenz mit zumindest 8 Aminosäuren und nicht mehr als 100 Aminosäuren einer immunodominanten Sequenz eines ersten Antigens oder einer mutierten Sequenz davon besteht, wobei die Sequenz durch ein Transplantationsantigen eingeschränkt ist, worin die Mutation zu größerer Übereinstimmung mit der Konsenssequenz eines durch das Transplantationsantigen eingeschränkten Agretops ist oder die erste Domäne aus einer Sequenz besteht, die im wesentlichen aus einer Sequenz mit zumindest 8 Aminosäuren und nicht mehr als 100 Aminosäuren eines polymorphen Bereichs des ersten Transplantationsantigens besteht;
mit der Maßgabe, daß, wenn die erste Domäne aus der immunodominanten Sequenz besteht, die Domäne mit einer zweiten Epitopstelle eines anderen Moleküls als das erste Antigen verbunden ist oder eine Epitopstelle des ersten Antigens durch eine andere als die natürliche Sequenz des ersten Antigens verbunden ist,
wobei die Zusammensetzung zur Verwendung bei einem Verfahren zum Modulieren des Immunresponses eines in vivo-Zellsystems in vivo zu einem Epitop des ersten Antigens bestimmt ist, auf das das Zellsystem immunologisch anspricht, wobei das Zellsystem durch ein erstes Transplantationsantigen eingeschränkte T-Zellen und das erste Transplantationsantigen umfassende Zellen umfaßt.

2. Zusammensetzung nach Anspruch 1, worin das Zellsystem Gesamtblut ist.

3. Zusammensetzung nach Anspruch 2, worin die mutierte Sequenz so mutiert ist, daß sie mit der Konsenssequenz des durch das Transplantationsantigen eingeschränkten Agretops übereinstimmt.

4. Zusammensetzung nach Anspruch 1, worin die erste Domäne aus einer Sequenz eines polymorphen Bereichs des Transplantationsantigens besteht.

5. Zusammensetzung nach Anspruch 1, worin die erste Domäne mit einer zweiten Epitopstelle verbunden ist.

6. Zusammensetzung nach Anspruch 1, die ein weiteres Molekül enthält, das eine erste Domäne aus einer Sequenz mit zumindest 8 Aminosäuren und nicht mehr als 100 Aminosäuren einer immunodominanten Sequenz des ersten Antigens oder eine mutierte Sequenz davon umfaßt, wobei die Sequenz durch ein Transplantationsantigen eingeschränkt ist, wobei die Mutation zu einer erhöhten Übereinstimmung mit der Konsenssequenz des durch ein zweites Transplantationsantigen eingeschränkten Agretops führt oder die erste Domäne aus einer Sequenz besteht, die im wesentlichen aus einer Sequenz mit zumindest 8 Aminosäuren und nicht mehr als 100 Aminosäuren eines polymorphen Bereichs des zweiten Transplantationsantigens besteht,
wodurch bei einem Immunrespone-Modulierungsverfahren das Zellsystem heterozygote T-Zellen umfaßt, die durch zumindest eines der ersten und zweiten Transplantationsantigene eingeschränkt sind und das erste Molekül fähig ist, sich an das erste Transplantationsantigen zu binden, und das zweite Molekül fähig ist, sich an das zweite Transplantationsantigen zu binden.

7. Zusammensetzung nach Anspruch 6, worin das Zellsystem Gesamtblut ist.